

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C. 20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 May 2000 (04.05.00)	
International application No. PCT/EP99/06298	Applicant's or agent's file reference FC 856
International filing date (day/month/year) 27 August 1999 (27.08.99)	Priority date (day/month/year) 14 September 1998 (14.09.98)
Applicant PACCIARINI, Maria, Adele et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

28 March 2000 (28.03.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer F. Baechler Telephone No.: (41-22) 338.83.38
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FC 856	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/06298	International filing date (day/month/year) 27/08/1999	Priority date (day/month/year) 14/09/1998
International Patent Classification (IPC) or national classification and IPC A61K31/70		
Applicant PHARMACIA & UPJOHN S.P.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 28/03/2000	Date of completion of this report 13.12.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giacobbe, S Telephone No. +49 89 2399 8463



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06298

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-14 as originally filed

Claims, No.:

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06298

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 18, 19.

because:

- ☒ the said international application, or the said claims Nos. 18, 19 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-19
	No: Claims
Inventive step (IS)	Yes: Claims
	No: Claims 1-19
Industrial applicability (IA)	Yes: Claims 1-17

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/06298

No: Claims 18, 19 (see Separate Sheet)

2. Citations and explanations
see separate sheet

1. Section III

Claims 18 and 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). However, although not required under the provisions of the PCT, an opinion will be given with respect to novelty and inventive step.

2. Section V

2.1 Cited Documents

The following documents (D) are referred to in this Report:

- D1: ROBERT, J. et al.: 'Pharmacokinetics and metabolism of anthracyclines' **CANCER SURVEYS**, vol. 17, 1993, pp. 219-252
- D2: KIRK, S. et al.: 'Irresectable hepatoma treated by intrahepatic iodized oil doxorubicin hydrochloride: Initial results' **SURGERY**, vol. 109(6), 1991, pp. 694-697
- D3: VASEY, P.A. et al.: 'Phase I clinical and pharmacokinetic study of 3'-deamino-3'-(2-methoxy-4-morpholinyl)doxorubicin (FCE 23762)' **CANCER RESEARCH**, vol. 55(10), 1995, pp. 2090-2096
- D4: QUINTIERI, L. et al.: 'Delivery of methoxymorpholinyl doxorubicin by interleukin 2-activated NK cells: Effect in mice bearing hepatic metastases' **BRITISH JOURNAL OF CANCER**, vol. 79(7-8), March 1999, pp. 1067-1073

The Applicant is informed that no check has been made as to whether priority has been validly claimed. Therefore document D4, which has been disregarded in writing the present Opinion, could become relevant for the assessment of novelty once the present application enters the regional phase (Rule 64(3) PCT).

2.2 Art 33(2) PCT (Novelty)

The subject-matter of present claims 1-19 meets the requirements of Art 33(2) PCT.

2.3 Art 33(3) PCT (Inventive step)

The subject-matter of claims 1-19 does not meet the requirements of Art 33(3) PCT.

Document D1, which is considered to represent the most relevant state of the art,

discloses (cf. from p. 228, l. 5 to the end of the chapter) that 'a common use of anthracyclines ... has been the treatment of hepatic tumours ...', possibly in formulations containing lipiodol. This idea is more closely described by document D2 (cf. e.g. Abstract), where doxorubicin is used, and is acknowledged by the Applicant (cf. p. 4, ll. 11-19). The technical problem which the present application sought to solve vis-à-vis these prior art documents can be formulated as "how to provide a different drug for the intrahepatic treatment of hepatic tumours". The solution proposed, i.e. the use of MMDX, can not be considered as involving an inventive step since the skilled person would have known from D3 (cf. Abstract) and D1 itself (cf. p. 240, Figure 3, last compound and p. 242, 'Summary', especially the last 4 lines) that this molecule is an anthracycline more active than its parent compound. He could have therefore combined these teachings without the use of any inventive ability, thereby coming to the proposed solution.

2.4 Art 33(4) PCT (Industrial applicability)

As stated above, no opinion is given on the question of whether present claims 18 and 19 are industrially applicable since their patentability is inter alia dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT.

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/70	A3	(11) International Publication Number: WO 00/15203 (43) International Publication Date: 23 March 2000 (23.03.00)
(21) International Application Number: PCT/EP99/06298 (22) International Filing Date: 27 August 1999 (27.08.99) (30) Priority Data: 9820012.4 14 September 1998 (14.09.98) GB (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milano (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): PACCIARINI, Maria, Adele [IT/IT]; Via degli Imbriani, 39, I-20158 Milano (IT). VALOTA, Olga [IT/IT]; Via Nazario Sauro, 99, I-20025 Legnano (IT). KERR, David [GB/GB]; 27 Westhill Road, Kings Norton, Birmingham B38 8TL (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 20 July 2000 (20.07.00)
(54) Title: USE OF METHOXYMORPHOLINO DOXORUBICIN FOR THE TREATMENT OF A LIVER TUMOR		
(57) Abstract		
<p>The present invention relates to the use of methoxymorpholino doxorubicin for the treatment of a liver cancer; in particular, it refers to the intrahepatic administration of methoxymorpholino doxorubicin for use in the liver tumor therapy optionally in association with an agent which remains selectively in liver tumor after its injection through the hepatic artery.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

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EE	Estonia						

INTERNATIONAL SEARCH REPORT

National Application No.

PCT/EP 99/06298

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	QUINTIERI, L. ET AL: "Delivery of methoxymorpholinyl doxorubicin by interleukin 2-activated NK cells: Effect in mice bearing hepatic metastases" BRITISH JOURNAL OF CANCER, vol. 79, no. 7-8, March 1999 (1999-03), pages 1067-1073, XP000893191 the whole document	1,4,5,8, 13,15, 16,18,19
X	VASEY, P.A. ET AL: "Phase I clinical and pharmacokinetic study of 3'-deamino-3'-(2-methoxy-4-morpholinyl)doxorubicin (FCE 23762)" CANCER RESEARCH, vol. 55, no. 10, 1995, pages 2090-2096, XP000891501 the whole document especially page 2091, Table 1	1-3,5, 10-12, 18,19

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☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

17 April 2000

Date of mailing of the international search report

03/05/2000

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/06298

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAUB, R.N. ET AL: "Phase II study of methoxymorpholinodoxorubicin in advanced sarcomas (PNU/S2243 (FCE 23762))" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY, vol. 16, 1997, page A1831 XP002135896 abstract	1,4-6, 18,19
X	BAKKER, M. ET AL: "Broad phase II and pharmacokinetic study of methoxy-morpholino doxorubicin (FCE 23762-MMRDX) in non-small-cell lung cancer, renal cancer and other solid tumour patients" BRITISH JOURNAL OF CANCER, vol. 77, no. 1, January 1998 (1998-01), pages 139-146, XP000893190 the whole document especially page 140, Table 1	1,4-6, 18,19
Y	ROBERT, J. ET AL: "Pharmacokinetics and metabolism of anthracyclines" CANCER SURVEYS, vol. 17, 1993, pages 219-252, XP000893095 page 228, line 4 -page 229, line 38 page 239, line 25 -page 242, line 23 especially page 242, line 15-17	1-5,8,9, 13-19
Y	ROUGIER, P. ET AL: "Intérêt des chimiothérapies loco-régionales par les anthracyclines" PATHOLOGIE BIOLOGIE, vol. 35, no. 1, 1987, pages 123-128, XP000893118 the whole document especially page 128, righthand column	1-5,8,9, 13-19
Y	KIRK, S. ET AL: "Irresectable hepatoma treated by intrahepatic iodized oil doxorubicin hydrochloride: Initial results" SURGERY, vol. 109, no. 6, 1991, pages 694-697, XP000893192 the whole document	1-5,8,9, 13-19
Y	CARR, B.I. ET AL: "Prolonged survival with chemotherapy alone for hepatocellular carcinoma (HCC) with intra-arterial chemotherapy" PROCEEDINGS OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY, vol. 13, March 1994 (1994-03), page 205 XP000893111 abstract	1-5,8,9, 13-19
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INTERNATIONAL SEARCH REPORT

nal Application No

PCT/EP 99/06298

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CARR, B.I. ET AL: "Phase II study of Spherex (degradable starch microspheres) injected into the hepatic artery in conjunction with doxorubicin and cisplatin in the treatment of advanced-stage hepaocellular carcinoma: Interim analysis" SEMINARS IN ONCOLGY, vol. 24, no. 2 suppl. 6, April 1997 (1997-04), pages S6-97-S6-99, XP000893102 the whole document</p>	<p>1-5,8, 13,15, 16,18,19</p>